REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

In item 2 on page 1 of the Office Action, the Examiner indicates the Action is a Final Rejection. PAIR also indicates the Action is a Final Rejection (see attached). Upon receipt and review of the Action, the undersigned endeavored to reach the Examiner by phone but was required to leave a voice mail message requesting issuance of a new Action because: i) the Action is marked "final" on its face but should have been marked "non-final" in view of the new ground of rejection not necessitated by the prior Amendment, and ii) the Action makes no reference to the Supplemental Amendment filed February 1, 2007. When the undersigned subsequently spoke with the Examiner, the Examiner refused to issue a new Action but acknowledged that the Action should have been marked "non-final". Further, the Examiner acknowledged receipt and entry of the Supplemental Amendment.

Despite the above verbal acknowledgments, the Examiner has not as yet issued any communication addressing the errors noted above. As Applicants have no choice but to rely on the written record, this Amendment and is being filed under Rule 116 and with an RCE. Once the Examiner has formally corrected the record as regards the non-finality of the April 20, 2007 Action, she is requested to take the steps necessary to ensure that the RCE fee is refunded to the undersigned firm's deposit account.

The undersigned hereby requests a personal interview with the Examiner and her supervisor prior to the issuance of any further Office Action. The Examiner is requested to cooperate with the undersigned in scheduling a mutually agreeable time for such an interview.

Claim 40 stands rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of that claim to correct the noted typographical error. Reconsideration is requested.

Claims 21, 22, 24-29, 34-36, 39 and 40 stand rejected under 35 USC 103 as allegedly being obvious over Schatz in view of either Derbyshire or Liu and Kauffman. The rejection is traversed.

It appears from the comments offered by the Examiner in response to Applicants prior arguments that the Examiner is confused by the reference teachings. Specifically, on page 6 of the Action, the Examiner indicates that claim 40 *"recites lambda phage 174 which includes the above lambda phage CI and cro repressors cited by Schatz above"*. However, there is no mention of a lambda phage anywhere in the claims. Claim 40, in fact, is directed to ϕX174. Lambda and ϕX174 are different phages: lambda (λ) is a double stranded phage whereas ϕX174 (phiX174) is a single stranded phage the genome of which has to be first converted into double stranded DNA prior to replication. The mention of lambda CI and cro repressors in Schatz has no relevance whatsoever to the invention presently claimed.

The Examiner also indicates that cis-binding is an inherent property of the DNA binding proteins disclosed by Schatz. This argument appears to be largely based on the confusion as regards lambda and phi phages.

In fact, none of the DNA binding proteins listed by Schatz are cis-acting, including lambda CI and cro repressors. Derbyshire lists three families of proteins that are cis-acting (i.e., DNA binding proteins that are not functional in complementation assays):

a. Bacterial transposases encoded by IS elements IS1, IS10, IS50 and IS903 and by transposing phage μ;

b. Replication proteins from some single stranded phage and plasmids (e.g. φX174 A protein and Rep A from plasmid R1);

c. Regulatory proteins such as anti-termination protein λQ and D-serine deaminase activator protein DscD.

The proteins that are listed by Schatz are highly characterized proteins and, if they were indeed cis-acting, they would undoubtedly have been cited as such by Derbyshire. Applicants have been unable to find any reports in the literature that suggest that any of the proteins disclosed by Schatz have cis activity.

Contrary to the suggestion of the Examiner, adding exogenous CI repressor to a cell harboring phage lambda would result in the expected repression, i.e. CI is capable of complementation, which is opposite from the non-complementation that defines cis-acting DNA binding proteins.

It is, therefore, submitted that Schatz does not, in fact, disclose the use of any cis-acting protein as required by the present invention.

The present invention has a number of advantages which would not have been possible, or predictable, based on the teachings of Schatz. The methods described in Schatz rely simply on the ability of a DNA binding protein to bind to a specific polynucleotide sequence. The use of a DNA binding protein as taught by Schatz would allow the polypeptide that is expressed to bind to a DNA molecule. However, Schatz does not provide any means to ensure that the polypeptide binds only to the specific DNA molecule that encoded it. The DNA binding proteins in Schatz have the potential to bind to the target polynucleotide sequence in any polynucleotide molecule.

This means that, for example, the method of Schatz cannot be used to produce multiple molecules in the same cell or solution, wherein each polypeptide is specifically attached only to the polynucleotide that encoded it.

If multiple polynucleotide molecules including a polynucleotide target sequence according to Schatz were expressed together in the same cell or solution, then the expressed polypeptides would each bind randomly to any of the polynucleotide molecules. The lack of cis-activity in the proteins of Schatz would result in proteins binding to the wrong templates: this means that the molecules produced would not necessarily comprise a polypeptide and the specific polynucleotide molecule that encoded it. Schatz offers no way in which binding only to the encoding polynucleotide can be ensured.

This is not the case when using the method of the present invention. The present invention makes use of cis-binding proteins. A cis-binding protein binds specifically to the polynucleotide molecule that encoded it. This means that, even if multiple different polynucleotides were expressed together in the same cell or solution, each polypeptide would bind only to the specific polynucleotide molecule that encoded it and not to other molecules in the solution, even if all the polynucleotide molecules had an identical sequence.

This allows, for example, a library of multiple different molecules to be produced simultaneously in a single cell or solution. As explained above, this would not be possible using the Schatz approach. Using the Schatz approach, a library of molecules could be produced only by generating each molecule separately in a different cell or solution and then mixing them.

The present invention also allows for the production of such molecules in a cell-free system. Again, this would not be possible using the Schatz approach. Schatz requires each

polynucleotide to be present as an expression vector, because of the need to express the polynucleotides within cells. This is not required when using a method of the present invention.

It can, therefore, be seen that the present invention has a number of advantages over the method described by Schatz. The methods are distinctly different and none of the other documents cited by the Examiner would have motivated the skilled reader of Schatz to carry out the method as claimed.

The Examiner has referred again to a passage on page 1261 of Derbyshire. It is again submitted that the Examiner has misunderstood this reference. The sentence quoted by the Examiner refers to a one thousand fold increase in efficiency. The Examiner appears to believe that this means that using a cis-acting protein would be one thousand fold more efficient than using a non cis-acting protein. That is not what Derbyshire says. The passage quoted by the Examiner in Derbyshire relates only to cis-acting proteins and how they can be best utilized in order to increase their efficiency. That is, this passage simply indicates that a cis-acting protein would be one thousand fold more efficient if its gene is located close to its binding site, than it would be if its gene was located further from its binding site. The comparison here is between the same cis-acting protein when located at different positions. There is no suggestion anywhere here of any advantage of cis-acting proteins over other DNA binding proteins. This simply teaches the skilled reader how best to use a cis-acting protein, once he/she has already decided that such a protein should be used.

In view of the above, reconsideration is requested.

Claims 21, 22, 24-29, 34-36, 39 and 40 stand rejected under 35 USC 103 as allegedly being obvious over Gold in view of Kauffman. This rejection is traversed.

A similar rejection under 35 USC 103 in relation to Gold was originally raised in the Office Action dated July 26, 2000. Applicants explained in the response to that Action, filed January 5, 2001, why the claimed methods would not have been obvious in view of the teachings of Gold. Those arguments were persuasive. Accordingly, it is not understood why the Examiner is raising similar objections seven years later.

As explained previously, the methods described in Gold are very different from those claimed in the present application. Gold is directed to methods wherein encoding mRNA remains attached to the ribosomes. Translation is stopped or stalled so that an isolated ribosome complex includes at least one ribosome, one peptide and the encoding mRNA. This is in contrast to the present invention. The instant claims clearly require that the peptides or proteins be specifically associated with the DNA encoding them through covalent binding. Gold does not describe any method involving binding of a protein to its encoding DNA. Rather, the system in Gold relies on binding of ribosomes to mRNA and the continued association of the encoded peptide to its mRNA via the ribosome.

The Examiner has referred again to the passage at page 9, lines 14 to 19 of Gold. As explained in the response of January 5, 2001, this passage refers to an "anchor" molecule that binds to the target molecule through a non-covalent interaction. It is clear from, for example, Figure 7 of Gold, showing interaction through an enzyme inhibitor or an enzyme substrate, that it is this anchor molecule that can be covalently linked, directly or indirectly to a bridge. There is no suggestion at all in Gold of DNA that encodes a protein which would bind to its encoding DNA through covalent binding.

As explained previously, therefore, the present invention would not have been obvious from the teachings of Gold. The passages referred to by the Examiner from Kauffman would not have brought one skilled in the art closer to the instant invention.

Kauffman refers to cis-acting nucleic acid elements and not to cis-acting DNA binding proteins as required by the claims. Cis-acting nucleic acid elements are DNA sequences that are acted upon in such a way that the activity of neighboring genes is in some way effected. An example of a cis-acting nucleic acid element is a promoter: binding of a transcription factor to the promoter can result in the transcription of the gene under the control of that promoter. Such elements are of course ubiquitous.

This is completely different from the cis-acting binding proteins recited in the instant claims. Cis-acting DNA binding proteins are, of course, proteins, not nucleic acid molecules. They are, therefore, structurally very different from cis-acting nucleic acid elements. Cis-acting DNA binding proteins are distinguished from other DNA binding proteins in the choice of DNA molecule to which they bind. Most DNA binding proteins, including the transcription factors which act on cis-acting nucleic acid elements, are able to diffuse through a cell or cell compartment and bind to any DNA molecule that contains the required binding site. As such, they are termed trans-acting. Only a very few DNA binding proteins will bind exclusively to the very same molecule of DNA that served as the template for their expression. It is this particular type of cis-activity that has been exploited in the current invention.

Accordingly, the disclosure of Kauffman in relation to cis-acting nucleic acid element is irrelevant to the present invention.

In view of the above, reconsideration is requested.

LINDQVIST et al
Appl. No. 09/331,808
October 22, 2007

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: Mary J. Wilson

Mary J. Wilson
Reg. No. 32,955

MJW:tat
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100